

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
21 May 2004 (21.05.2004)

PCT

(10) International Publication Number  
**WO 2004/042024 A3**

(51) International Patent Classification<sup>7</sup>: **C07H 21/04**,  
A61K 48/00, C12N 15/00

(21) International Application Number:  
PCT/US2003/034826

(22) International Filing Date: 31 October 2003 (31.10.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/423,262 1 November 2002 (01.11.2002) US

(71) Applicant (for all designated States except US): **THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA** [US/US]; 3160 Chestnut Street, Suite 200, Philadelphia, PA 19104 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **REICH, Samuel**, Jotham [US/US]; 312 Kent Road, Bala Cynwyd, PA 19004 (US). **SURACE, Enrico, Maria** [IT/IT]; Largo Della Crocetta 2, I-20122 Milan (IT). **TOLENTINO, Michael, J.** [US/US]; 474 South Ithan Avenue, Villanova, PA 19085 (US).

(74) Agents: **FRANK, George, A.** et al.; Drinker Biddle & Reath LLP, One Logan Square, 18th and Cherry Streets, Philadelphia, PA 19103-6996 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**

- with international search report
- with amended claims

(88) Date of publication of the international search report:  
23 September 2004

Date of publication of the amended claims: 11 November 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMPOSITIONS AND METHODS FOR siRNA INHIBITION OF HIF-1 ALPHA

(57) Abstract: RNA interference using small interfering RNAs which target HIF-1 alpha mRNA inhibit expression of the HIF-1 alpha gene. As HIF-1 alpha is a transcriptional regulator of VEGF, expression of VEGF is also inhibited. Control of VEGF production through siRNA-mediated down-regulation of HIF-1 alpha can be used to inhibit angiogenesis, in particularly in diseases such as diabetic retinopathy, age related macular degeneration and many types of cancer.



WO 2004/042024 A3

**AMENDED CLAIMS**

[received by the International Bureau on 30 August 2004 (30.08.04);  
original claims 1-77 unchanged ; new claims 78-79 added ; (1 page)]

76. The method of claim 67, wherein the siRNA is administered to a subject in combination with another therapeutic method designed to treat the angiogenic disease.

77. The method of claim 76, wherein the angiogenic disease is cancer, and the siRNA is administered in combination with radiation therapy, chemotherapy or surgery.

78. The siRNA of claim 1, wherein the siRNA further comprises altered RNA.

79. The siRNA of claim 7, wherein one or more nucleotides in the siRNA are substituted with deoxyribonucleotides.